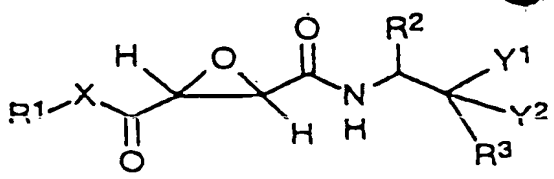


(1)

T0620

wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

P1

R^2 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^3 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

X represents -O- or -NR^4- in which R^4 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl

62 D

group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

Y^1 represents a hydroxyl group, an alkoxy group having 1 to 6 carbon atoms, an acetoxy group, or an aralkyloxy group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

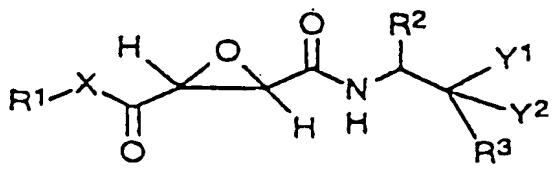
Y^2 represents a hydrogen atom or an alkyl group having 1 to 10 carbon atoms;

provided that the aryl group for R^1 to R^4 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxy-carbonyl having 2-7 carbon atoms, $-CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino; and

provided that the heterocyclic group for R^3 and R^4 is selected from the group consisting of pyridyl, pyrrolidinyl, piperidinyl, furyl, thienyl, piperazinyl, indolyl and benzimidazolyl.

7 ~~28~~. (Thrice Amended) An epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt:

T0630



(1)

63

wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an isobutyl group or an isopropyl group;

R^3 represents a hydrogen atom or an aryl group having 6 to 20 carbon atoms;

X represents -O- or $-NR^4-$ in which R^4 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

02

Y^1 represents OR^5 in which R^5 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, an acetoxy group, a benzoyloxy group, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom;

provided that the alkyl group for R^5 may have one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, $-CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, and guanidino;

64 D

provided that the aryl group for R^1, R^3 and R^5 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, $-CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino;

P2

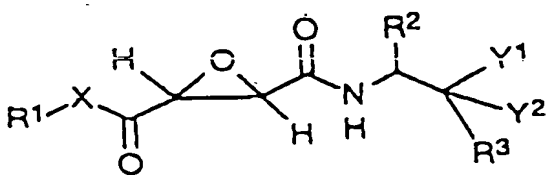
provided that the heterocyclic group for R^5 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, $-CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino; and

provided that the heterocyclic group for R^3, R^4 and R^5 is selected from the group consisting of pyridyl, pyrrolidinyl, piperidinyl, furyl, thienyl, piperazinyl, indolyl and benzimidazolyl.

12

~~32~~. (Twice Amended) A method for treating a bone disease selected from the group consisting of osteoporosis, malignant hypercalcemia and Paget's disease, the method comprising injecting or orally administering into a patient an epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt in an amount of 0.01 to 100 mg/day in the case of injection or in an amount of 0.1 mg/day to 1 g/day in the case of oral administration:

D3



(1)

T0660

wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^3 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

X represents -O- or -NR^4- in which R^4 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl

group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

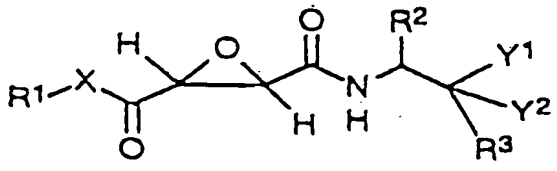
Y^1 represents a hydroxyl group, an alkoxy group having 1 to 6 carbon atoms, an acetoxy group, or an aralkylaxy group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom or an alkyl group having 1 to 10 carbon atoms;

provided that the aryl group for R^1 to R^4 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, $-CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino; and

provided that the heterocyclic group for R^3 and R^4 is selected from the group consisting of pyridyl, pyrrolidinyl, piperidinyl, furyl, thienyl, piperazinyl, indolyl and benzimidazolyl.

~~13~~ 12. (Twice Amended) A method for treating arthritis which comprises injecting or orally administering into a patient an epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt in an amount of 0.01 to 100 mg/day in the case of injection or in an amount of 0.1 mg/day to 1 g/day in the case of oral administration:



(1)

Serial No. 09/508,026
September 7, 2001

wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

D3

R^3 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

X represents -O- or $-NR^4-$ in which R^4 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

Y^1 represents a hydroxyl group, an alkoxy group having 1 to 6 carbon atoms, an acetoxy group, or an aralkyloxy group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom or an alkyl group having 1 to 10 carbon atoms;

provided that the aryl group for R^1 to R^4 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxy-carbonyl having 2-7 carbon atoms, $-CONH_2$, alkylamino-carbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino; and

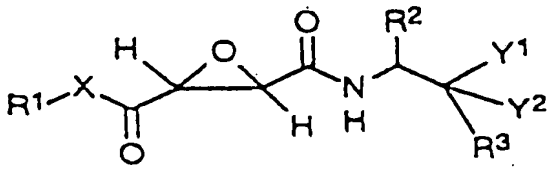
provided that the heterocyclic group for R^3 and R^4 is selected from the group consisting of pyridyl, pyrrolidinyl, piperidinyl, furyl, thienyl, piperazinyl, indolyl and benzimidazolyl.

03

14

34. (Thrice Amended) A method for treating a bone disease selected from the group consisting of osteoporosis, malignant hypercalcemia and Paget's disease, the method comprising injecting or orally administering into a patient an epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt in an amount of 0.01 to 100 mg/day in the case of injection or in an amount of 0.1 mg/day to 1 g/day in the case of oral administration:

T0690



(1)

wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms,

an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an isobutyl group or an isopropyl group;

R^3 represents a hydrogen atom or an aryl group having 6 to 20 carbon atoms;

X represents -O- or $-NR^4-$ in which R^4 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

Y^1 represents OR^5 in which R^5 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, an acetoxy group, a benzoyloxy group, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom;

provided that the alkyl group for R^5 may have one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, $-CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, and guanidino;

provided that the aryl group for R^1, R^3 and R^5 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total,

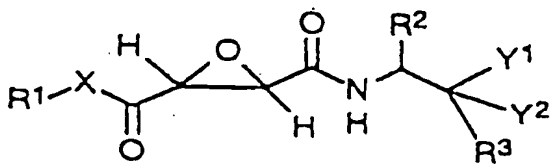
alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, -$CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino;

provided that the heterocyclic group for R^5 may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, -$CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino; and

provided that the heterocyclic group for R^4 and R^5 is selected from the group consisting of pyridyl, pyrrolidinyl, piperidinyl, furyl, thienyl, piperazinyl, indolyl and benzimidazolyl.

15

38. (Thrice Amended) A method for treating arthritis which comprises injecting or orally administering into a patient an epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt in an amount of 0.01 to 100 mg/day in the case of injection or in an amount of 0.1 mg/day to 1 g/day in the case of oral administration:



(1)

wherein

R^1 represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R^2 represents an isobutyl group or an isopropyl group;

R^3 represents a hydrogen atom or an aryl group having 6 to 20 carbon atoms;

X represents -O- or $-NR^4-$ in which R^4 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

D3

Y^1 represents OR^5 in which R^5 is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group consisting of an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, an acetoxy group, a benzoyloxy group, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group consisting of a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y^2 represents a hydrogen atom;

provided that the alkyl group for R^5 may have one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, $-CONH_2$, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, and guanidino;

72 D